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SUCCESSFUL TREATMENT OF METASTATIC LUNG ADENOCARCINOMA WITH LAZERTINIB: A CASE REPORT

O. Vynnychenko[1], V. Kovchun[2]

[1] Sumy Regional Council Municipal Non-Profit Enterprise «Sumy Regional Clinical Oncology Center», Sumy, Ukraine; [2]Department of Oncology and Radiology, Sumy State University, Sumy, Ukraine

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E-mail:
vynnychenkool@ukr.net
vu.kovchun@med.sumdu.edu.ua

Abstract. *Lung cancer is one of the most common social diseases affecting the quality and length of life. A feature of lung cancer is the high frequency of genetic mutations. EGFR mutation is the most common among them. The prognosis for patients, especially with advanced stages, remains unfavorable since this type of tumor is resistant to chemotherapy. Tyrosine kinase inhibitors (TKIs) are considered the promising direction of targeted therapy. Gefitinib, afatinib, and erlotinib are TKIs widely used to treat patients. However, the significant problem remains the acquired resistance, which is most often associated with the additional mutation T790M. Lazertinib is a new and most promising third-generation EGFR-TKI.*

The study aimed *to investigate the indications for lazertinib and to report the results of the successful treatment of a patient with metastatic lung adenocarcinoma with a follow-up period of 35 months.*

Case report and discussion. *Lazertinib is used to treat patients with single (L858R, Ex19del, or T790M) or combined mutations (L858R and T790M, Ex19del and T790). This drug is effective for the first, second, and third lines of therapy, as it can block the T790M mutation, penetrate the blood-brain barrier, and counteract the emergence of acquired resistance. Lazertinib is used as monotherapy, but treatment effectiveness increases if combined with chemotherapy and/or amivantamab (a bispecific antibody against EGFR and MET). Our case report demonstrates that progression-free survival in patients receiving lazertinib can be very high. In patients taking tyrosine kinase inhibitors of the first generation, disease progression occurs after about 12 months. In our case, the patient has no progression within 35 months of treatment. Skin dryness and grade 1 thrombocytopenia have been reported as side effects. The high efficiency of lazertinib in the presented case report can be explained by the presence of the most sensitive to EGFR-TKI mutation - Ex19del, and the absence of uncommon mutations such as Ex20ins, G719X, L861Q, S768I, and T790M.*

Conclusions. *Lazertinib is a highly effective EGFR-TKI with a low toxicity profile that may significantly improve the treatment outcomes of EGFR-mutated patients.*

УСПІШНЕ ЛІКУВАННЯ МЕТАСТАТИЧНОЇ АДЕНОКАРЦИНОМИ ЛЕГЕНЬ ЛАЗЕРТИНІБОМ: ВИПАДОК ІЗ ПРАКТИКИ

О.І. Винниченко, В.Ю. Ковчун

Ключові слова: *лазертиніб, рак легень, виживання, інгібітори тирозинкінази.*

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Резюме. *Рак легень - один із найактуальніших соціальних захворювань, що впливає на якість і тривалість життя. Особливістю раку легень є висока частота генетичних мутацій. Найпоширеніша серед них - мутація EGFR. Прогноз для хворих, особливо при запущених стадіях, залишається несприятливим, оскільки даний вид пухлини стійкий до хіміотерапії. Інгібітори тирозинкінази (ІТК) вважаються перспективним напрямком таргетної терапії. Гефітиніб, афатиніб і ерлотиніб є ІТК, які широко використовуються для лікування пацієнтів. Однак істотною проблемою залишається набута резистентність, яка найчастіше пов'язана з додатковою мутацією Т790М. Лазертиніб - новий і найбільш перспективний EGFR-TKI третього покоління.*

Дослідження мало на меті вивчити показання до лазертинібу та повідомити про результати успішного лікування пацієнта з метастатичною аденокарциномою легень з періодом спостереження 35 місяців.

Розповідь про випадок та обговорення. *Лазертиніб використовується для лікування пацієнтів з одиночними (L858R, Ex19del або T790M) або комбінованими мутаціями (L858R і T790M, Ex19del і T790). Цей препарат ефективний для першої, другої та третьої лінії терапії, оскільки здатний*

блокувати мутацію T790M, проникати через гематоенцефалічний бар'єр та протидіяти виникненню набутої резистентності. Лазертиніб використовується як монотерапія, але ефективність лікування підвищується в поєднанні з хіміотерапією та/або амівантамабом (біспецифічні антитіла проти EGFR і MET). Наш випадок із практики демонструє, що виживаність без прогресування у пацієнтів, які отримують лазертиніб, може бути дуже високою. У пацієнтів, які приймають інгібітори тирозинкінази першого покоління, прогресування захворювання відбувається приблизно через 12 місяців. У нашому випадку в пацієнта не спостерігається прогресування протягом 35 місяців лікування. Як побічні ефекти повідомлялося про сухість шкіри та тромбоцитопенію 1 ступеня. Високу ефективність лазертинібу в представленому випадку можна пояснити наявністю найбільш чутливої до EGFR-TKI мутації Ex19del та відсутністю нестандартних мутацій, таких як Ex20ins, G719X, L861Q, S768I та T790M.

Висновки. *Лазертиніб є високоефективним EGFR-TKI з низьким профілем токсичності, який може значно покращити результати лікування пацієнтів із мутацією EGFR.*

Introduction. In 2022, there were 2,480,301 new cases and 1,817,172 deaths from lung cancer worldwide. This malignant neoplasm is one of the most common social diseases affecting the quality and length of life [1]. Adenocarcinoma is considered the main histological variant of lung cancer. Most patients are in the advanced stage at the time of diagnosis, so the five-year survival rate is extremely low (15%). The development of adenocarcinoma can be associated with smoking, but it is also quite common in people who have never smoked [2]. A feature of lung adenocarcinoma is the high frequency of genetic mutations, such as anaplastic lymphoma kinase (ALK), epidermal growth factor receptor (EGFR), Kirsten rat sarcoma virus (KRAS), receptor tyrosine kinase (RET), mouse sarcoma viral oncogene homolog B1 (BRAF). The most common among them is a mutation in the EGFR gene. In about 50-60% of patients from the Asian region, lung adenocarcinoma is associated with this particular gene defect. The genetic component is the main reason for resistance to chemotherapy and low patient survival [3].

Epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) are targeted drugs that have become a real breakthrough in clinical oncology due to significant improvements in patient outcomes. EGFR-TKIs are used for a confirmed mutation in exons 19 or 21 [4]. For the first line of therapy, afatinib, gefitinib, and erlotinib are most often used, but acquired resistance appears in less than 12 months. The leading cause of this phenomenon is the occurrence of an additional T790M mutation in about 55% of patients [5, 6].

Lazertinib is a modern third-generation EGFR-TKI capable of penetrating the blood-brain barrier. This drug inactivates EGFR L858R and Ex19del mutations. In addition, it is effective in the case of the T790M mutation, which is why it received the first approval from the FDA in 2021 [7].

The study aimed to investigate the indications for lazertinib and to report the successful treatment of a patient with metastatic lung adenocarcinoma with a follow-up period of 35 months.

Case report. A 69-year-old male patient visited the Sumy Regional Clinical Oncology Center (Ukraine) in June 2021 due to pelvis and lower limbs pain, periodic dry cough, and progressive shortness of breath. After computed tomography (CT) with contrast, the presence of a tumor of the upper lobe of the right lung, metastases in the axillary lymph node on the right, the ischial bone on the right, and the iliac bone on the left (T2N2M1c) were established. A bronchoscopy with biopsy was performed. Pathohistological examination revealed the presence of highly differentiated adenocarcinoma. The patient confirmed the presence of a family predisposition to the development of oncological diseases and denied a history of smoking. After this, we suspected the presence of a genetic mutation, so a sample of tumor tissue in the form of a paraffin block was sent to Dila's laboratory (Kyiv) for research on the most common mutations (EGFR and ALK). According to the study results, the tumor tissue was positive for the EGFR mutation. Extended analysis confirmed a deletion in exon 19 (Ex19del). Insertion 20 (Ex20ins), mutations G719X, L858R, L861Q, S768I and T790M were not found.

To reduce the total volume of tumor tissue, in June 2021, the patient underwent an extended right upper lobectomy. In July 2021, to relieve the pain due to the presence of metastases in the bones of the pelvis, a palliative course of radiation therapy was prescribed (total dose of 18 Gy), and a course of targeted therapy of Lazertinib 240 mg per day without interruptions was started. In addition, every four weeks, the patient was administered zoledronic acid at a dose of 4 mg intravenously. At the time of the initiation of treatment, the patient's general condition corresponded to ECOG 2.

CT scans were repeated every six weeks for the first 18 months from the start of treatment and every 12 weeks after that. The results were evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST1.1). After the first six weeks, the patient's general condition improved and corresponded to ECOG 1. According to CT data, the axillary lymph node on the right completely disappeared, and the size of metastatic lesions in the pelvic bones decreased. Treatment was continued in the same doses. The patient noted skin dryness as the single side effect of lazertinib. The hematological toxicity was not higher than grade 1 thrombocytopenia, which first appeared two months after the start of therapy and continues to this day. This condition did not need any management.

Currently, the patient continues treatment. According to RECIST1.1, a partial response was registered. A single lesion remains in the pelvic bones. Before treatment, it was

lytic ilium metastases with a size of 44 x20 mm. Therapy with lazertinib and zoledronic acid stimulated bone structure restoration due to bone matrix formation. Images of the ilium metastasis according to the CT in dynamic can be seen in Fig. 1. The patient's general condition corresponds to ECOG 0. The progression of the disease was not registered. After 36 months of treatment, the patient will continue a CT scan every six months.

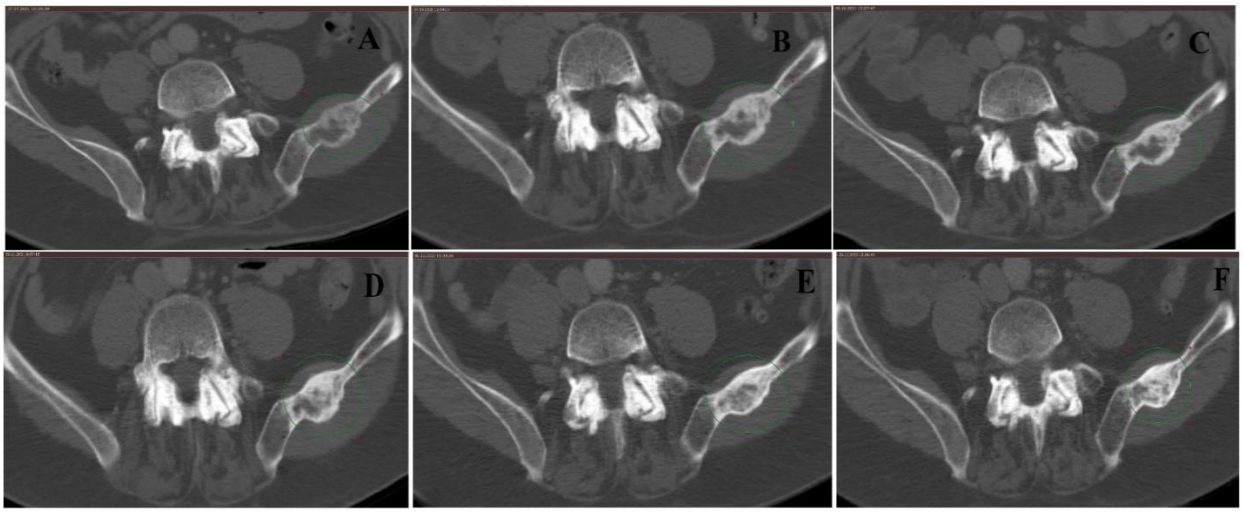

Figure 1. Images of the ilium metastasis according to the CT. A – before targeted therapy, B - after 1,5 months, C – after 3 months, D – after 4,5 months, E – after 15,5 months, F - after 30 months

Discussion. Lazertinib is a new and most promising third-generation EGFR-TKI. It can be used for single (e.g., L858R, Ex19del, or T790M) or combined mutations (e.g., L858R and T790M, Ex19del and T790) [7]. The phase III study LASER301 compared the efficacy and safety of lazertinib and gefitinib. Three hundred ninety-three patients with untreated locally advanced or metastatic non-small cell lung cancer received targeted therapy. Median progression-free survival was significantly higher in the lazertinib group (20.6 vs. 9.7 months) [8].

This targeted drug has demonstrated efficacy in patients with disease progression after first-line therapy. Kim et al. [9] investigated the effectiveness of lazertinib as a second and third-line therapy. The objective response and disease control rates were 62.1% and 94.2%, respectively.

Osimertinib, currently widely used as a first-line therapy for EGFR-mutated lung adenocarcinoma, is considered an analog of lazertinib. However, in treatment with osimertinib, new mutations occur, leading to resistance and relapse of the disease [10]. This fact prompts the researchers to use new targeted drugs and combined therapy regimens. The MARIPOSA study examined the efficacy and safety of the combination of lasertinib and amivantamab (a bispecific antibody against EGFR and MET alterations) for the treatment of patients with EGFR-mutated metastatic non-small cell lung cancer. The results were compared with the group of patients taking osimertinib. As a result, it was confirmed that progression-free survival was 7.1 months longer in patients receiving lazertinib and amivantamab [11].

The MARIPOSA-2 study enrolled patients with confirmed disease progression after receiving osimertinib. The amivantamab/chemotherapy and amivantamab/lasertinib/chemotherapy groups had significantly better median progression-free survival than the chemotherapy group (12.5 and 12.8 months vs. 8.3 months) [12].

Lazertinib has a low toxicity profile. The most common side effects are rash, diarrhea, pruritus, and paresthesia. They were registered in 54%, 47%, 35% and 35% of cases, respectively. The pruritus and rash corresponded to the 1st and 2nd grades. Grade 3 paresthesia and diarrhea were reported in 2% and 7% of cases [13].

Jang et al. [14] evaluated the cardiotoxicity of lazertinib, including QT prolongation, left ventricular ejection fraction reduction, and heart failure. None of the 181 patients had clinically significant decreases in left ventricular ejection fraction or QT prolongation. Heart failure of the 2nd degree developed in 1 patient. As a result, scientists concluded that the cardiac risk in patients treated with lazertinib is low.

We report a clinical case of a patient with metastatic lung adenocarcinoma with a single Ex19del mutation who did not have resistance to lazertinib during 35 months of follow-up. The results of this patient's treatment confirm the efficacy of this third-generation EGFR-TKI as a first-line therapy. Survival without progression significantly exceeds the data in the LASER301 study (20.6 months versus 35 months) [8]. Similar to the results of Jang et al. [14], we did not detect any cardiotoxic effect of lazertinib. Dryness of the skin and grade 1 thrombocytopenia were the only adverse effects reported in our patient directly attributable to the targeted therapy.

The high efficiency of lazertinib in the presented case report can be explained by the presence of the most sensitive to EGFR-TKI mutation - Ex19del. Patients with Ex19del have significantly better progression-free survival and overall survival than those with uncommon mutations such as Ex20ins, G719X, L861Q, S768I, and T790M [15]. In addition, lazertinib penetrates the blood-brain barrier. The brain can be a "shelter" for tumor cells, allowing them to avoid drugs' therapeutic effects. Lazertinib can probably affect existing brain metastases [16] and prevent their appearance.

Conclusions. Our case report demonstrates that lazertinib is a highly effective EGFR-TKI with a low toxicity profile. This drug can significantly improve the treatment outcomes of EGFR-mutated patients.

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Conflict of interest. The authors declare no conflict of interest.

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Information about the authors

Vynnychenko OI - PhD, oncologist of Sumy Regional Clinical Oncology Center, Sumy, Ukraine. ORCID ID: https://orcid.org/0000-0001-5651-0323

Kovchun VYu - PhD, Assistant Professor, Department of Oncology and Radiology, Sumy State University, Sumy, Ukraine. ORCID ID: https://orcid.org/ 0000-0002-9577-0272

Відомості про авторів

Винниченко О.І. - канд.мед.наук, хірург-онколог КНП СОР Сумського обласного клінічного онкологічного центру, м. Суми, Україна. ORCID ID: https://orcid.org/0000-0001-5651-0323

Ковчун В.Ю. - канд.мед.наук, асистент, кафедра онкології та радіології Сумського державного університету, м. Суми, Україна. ORCID ID: https://orcid.org/ 0000-0002-9577-0272

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